World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

A REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM FOR ANTIHYPERTENSIVE DRUG

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Article Received on 28/03/2020 **Article Revised on 18/04/2020** **Article Accepted on 08/05/2020**

ABSTRACT

Hypertension is one of the largest death causing disease today. since, it is a chronic disease it requires long term treatment. As the antihypertensive drugs have certain disadvantages like more frequent administration, extensive first pass metabolism and variable bioequailability which make it an ideal candidate for Transdermal drug delivery system. The aim of this article is to review antihypertensive transdermal patches in perspective of enhancing the bioavailability and improving patient compliance. TDDS are topically administerded medicament. These transdermal patches are pharmaceutical preparation of varying sized containing one or mpre API and delivers the drug to systemic circulation.

KEYWORDS: Transdermal Patches, Hypertension, Antihypertensive.

1. INTRODUCTION

Transdermal Patches are used to deliver/administer a specific dose of medication through the skin and then into bloodstream. they were first approved in 1981 by FDA. The Transdermal delivery systems which is currently available contains scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerine for cardiovascular disease nicotine to aid smoking cessation, fentanyl for chronic pain.[1]

The Transdermal drug delivery system (TDDS) are defined as self contained, discrete dosage forms, which is when applied to the skin has the property to deliver the drug, through the skin to systemic circulation on a controlled rate.[2]

There are various of using TDDS such as in sustained drug delivery elimination of first pass metabolism, reduce side effects, reduce frequency of administration and improved patient compliance.[2]

Hypertension is a major health problem worldwide. It is a cardiovascular disease which caused 2.3 million deaths in india in year 1990; This is predicted to double by the year 2020. Hypertension is directly responsible for 57% of all strock deaths and 24% of all coronary heart disease deaths in india.

There e is a strong correlation between changing lifestyle factors and increase in Hypertension in india. Studies shows that hypertension in india is subjected to 25% urban and 10% rural subjects Therefore cost effective approaches to control blood pressure or hypertension among Indians is needed. Transdermal system are very useful for those diseases which requires chronic treatment.

Despite the effectiveness and great usefulness of TDDS in the treatment of chronic disease like hypertension ,cost of the antihypertensive patches is quite high then the conventional products. Despite high cost of these transdemal patches for the treatment of hypertention antihypertensive patches with the established dosages forms reduced the need of hospitalization and diagnostic costs.these advantages of antihypertensive patches increases the consumers acceptance as a costlier alternative to the conventionsal therapy. The first antihypertensive drug was clonidine to developed in transdermal form. Now, There are number of antihypertensive transdermal patches in the pharmaceutical market.

1.1 Advantages of Tdds

1. IT delivers a steady infusion of the drug over an extended periods of time. adverse effects and therapeutic failure can be avoided
2. TDDS increases the therapeutic value of many drugs by avoiding specific problems associated with the drug.
3. Self medication is possible with this types of system.

4. The simplified medication regimen leads to an improved patient compliance and reduce inter patient and intra patient variability.
5. The drug input can be terminated at any point of time by remaining the patch.

1.2 Disadvantages of Tdds

1. The drugs, the adhesive or other excipient in the patch formulation can cause erythema, itching, and local edema.
2. Allergic reaction may occurs.
3. It is essential in TDDS to have molecular
4. At the side of application, There are possibilities of local irritation.
5. The drug, the adhesive, or other excipient in the patch can some times cause erythema, itching and local edema etc.

2-Enhancing Transdermal Drug Delivery Skin Permeation

Through various investigations the utility of skin as a route for systemic administration was found skin is the most intensive and easily accessible organ of the human body. The barrier function of the skin is primarly provided by the stratum corneum (SC), the outermost layer of skin. Therefore, difference in permeability of drug through skin among species have been observed and compared by means of skin structural features such as the thickness of skin layers.

The thickness of the outermost layer stratum corneum is important to determine permeability coefficient and skin permeation flux and it also to estimate the blood and skin concentration of the applied drug.

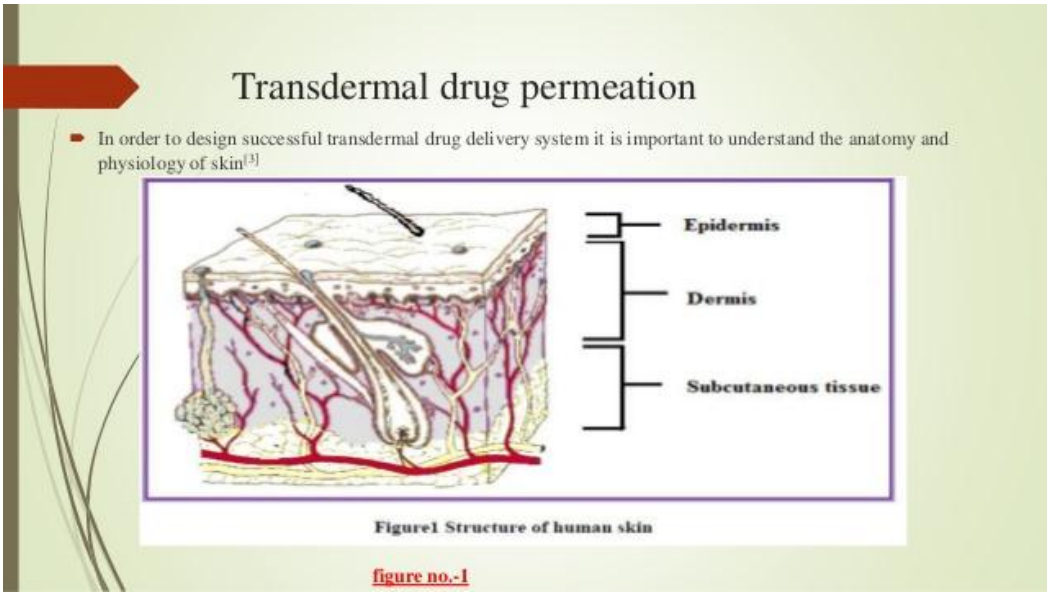

Figure 1: Structure of human skin.

3-Formulation Aspects of Transdermal Drug Delivery System

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

3.1 Polymer matrix / Drug reservoir- Polymers are the heart of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have good stability and compatibility with the drug and other components of the system and they should provide effective released of a drug throughout the device with safe status.[3]

3.1.1 The polymers used for TDDS can be classified as

3.1.1.1 Natural polymers: e.g. cellulose derivatives, zein, gelatine, shellac, waxes, gums, natural rubber and chitosan etc.

3.1.1.2 Synthetic elastomers: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber etc.

3.1.1.3 Synthetic polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.

The polymers like polyethylene glycol,[4] eudragits,[5] ethyl cellulose, polyvinylpyrrolidone,[6] and hydroxypropyl methylcellulose,[7] are used as matrix type TDDS.

3.2 Selection of drugs- The selection of drug for TDDS is based on physicochemical properties of drug.

Transdermal drug delivery system is much suitable for drug having.[8,9]

- Extensive first pass metabolism.
- Narrow therapeutic window.
- Short half-life which causes non-compliance due to frequent dosing.
- Dose should be less (mg/day).[10]
- Low molecular weight (less than 500 Daltons).
- Adequate solubility in oil and water (log P in the range of 1-3).
- Low melting point (less than 200°C).

3.3 Permeation enhancers- These compounds are useful to increase permeability of stratum corneum by interacting with structural components of stratum corneum i.e., proteins or lipids to attain higher therapeutic levels of the drug.[11] They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability.[12]

Some example are Dimethyl sulfoxide, Propylene glycol, 2-Pyrrolidone, Isopropyl myristate, Laurocapram (Azone), Sodium lauryl sulfate, Sorbitan monolaurate, Pluronic, Cardamom oil, Caraway oil, Lemon oil, Menthol, dlimonene, Linoleic acid.[13]

3.4 Pressure sensitive adhesives- The pressure-sensitive adhesive (PSA) affixes the Transdermal drug delivery system firmly to the skin. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue 28, 29. Adhesives must be skin-compatible, causing minimal irritation or sensitization, and removable without inflicting physical trauma or leaving residue.[14,15] In addition, they must be able to dissolve drug and Excipient in quantities sufficient for the desired pharmacological effect without losing their adhesive properties and skin tolerability. PSAs used in commercially available Transdermal systems include polyacrylate, polyisobutylene, and polysiloxane. Polyacrylates, are most widely used. In general, all acrylic adhesives are polar in character, allowing them to absorb moisture readily and to maintain adhesion to wet skin. They also dissolve most drugs well, enabling high drug loading of polyacrylate matrices. Polyisobutylenes (PIBs), in contrast, are characterized by a low solvent capacity for drugs. Similar to PIBs, silicones dissolve most drugs poorly and regulate tackiness and cohesion through polymer size. Molecular weight of silicones, however, can be hard to control during storage of drug-adhesive formulations, since drugs containing amine groups can catalyze further polymerization in silicone adhesives retaining residual silanol groups. To address this problem, special silicones have been developed that are rendered resistant to amine-catalyzed condensation through end-capping of silanol functional groups. Hot Melt Pressure Sensitive Adhesives (HMPSA), HMPSA melt to a viscosity suitable for coating, but when they are cooled they generally stay in a flowless state. They are thermoplastic in nature. Compounded HMPSA are Ethylene vinyl acetate copolymers, Paraffin waxes, Low density polypropylene, Styrene-butadiene copolymers, Ethylene-ethacrylate copolymers. Uncompounded HMPSA are Polyesters, Polyamides and Polyurethanes.

3.5 Backing laminate- Backing materials must be flexible while possessing good tensile strength. Commonly used materials are polyolefin's, polyesters, and elastomers in clear pigmented, or metallized form. Elastomeric materials such as low-density polyethylene conform more readily to skin movement and provide better adhesion than less compliant materials such as polyester. Backing materials should also have low water vapour transmission rates to promote increased skin hydration and, thus, greater skin permeability. In systems containing drug within a liquid or gel, the backing material must be heat-sealable to allow fluid-tight packaging of the drug reservoir using a process known as form-fill-seal. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapour transmission rate.[16,17] Examples of some backing materials are vinyl, polyester films, Polyester-polypropylene films, Polypropylene resin, Polyethylene resin, Polyurethylene, Co Tran 9722 film, Ethylene-vinyl acetate, Aluminized plastic laminate.

3.6 Release Liner -During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metalised laminates.[15,18]

3.7 Other excipients- Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir.[19] In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.[19,20]

4-Various methods for preparation of TDDS

4.1 Circular teflon mould method (Baker and Heller 1989)

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent.

Enhancers different concentrations are dissolved in the other half of the organic solvent and then added. Plasticizer (e.g., Di-N-butylphthalate) is added into the drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. The moulds are to be placed on a levelled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are to be stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. These types of films are to be evaluated within one week of their preparation. Alanazi et al., (2007) have studied about bioadhesive film containing ketorolac. Films were cast from organic and aqueous solvents using various bioadhesive polymers namely: sodium carboxymethyl cellulose (Na-CMC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) and Carbopol 934. The prepared films were subjected to investigations for their physical and mechanical properties, swelling behaviours, in-vitro bioadhesion, drug permeation via bovine buccal mucosa and in-vitro drug release. These properties were found to vary significantly depending on the preparation methods, the type of the polymers and the ratio of addition of both plasticizer (i.e. polyethylene glycol) and film forming agent (ethyl cellulose and polyvinylpyrolidene). The obtained results indicated that the concentration of ketorolac in the oral cavity was maintained above 4.0 µg/mL for a period of at least 6 h. This film showed promising results for using the ketrolac buccoadhesive route of administration topically and systemicall.

4.2 Asymmetric TPX membrane method (Berner and John 1994)

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive. These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath (maintained the temperature at 25°C). After 10 minutes of immersion, the membrane can be removed, air dried in a circulation oven at 50°C for 12 h. Wang et al., (1998) have studied that asymmetric poly(4-methyl-1-pentene) (TPX) membranes, fabricated by the dry/wet inversion method, were applied to transdermal delivery of nitroglycerin (NTG), a drug for treating angina pectoris. The flux of NTG through the TPX membrane was measured in-vitro by a Franz cell. The results indicated that the NTG flux through asymmetric TPX membranes is strongly dependent on the membrane structure, which can be varied by adding non solvents in the casting solution. By adding different kinds of non solvents and adjusting the added amounts, membranes with different NTG-release rates can be fabricated. It was also found that, with suitable drug formula, the NTG dissolution rate of a prototype TPX patch is comparable to that of a commercial patch, Transderm-Nitro.

4.3 Mercury substrate method

The drug is dissolved in polymer solution along with plasticizer. It is followed by stirring for 10- 15 minutes to produce a homogenous dispersion and poured into a levelled mercury surface, covered with inverted funnel to control solvent evaporation (Wiechers 1992). Rathore et al., (2006) have studied that transdermal matrix type patches of terbutaline sulphate were fabricated using ethyl cellulose and cellulose acetate polymer. The transdermal patches of terbutaline sulphate were prepared by solvent casting technique employing a mercury substrate. In the present investigation various polymeric transdermal patches of terbutaline sulphate were prepared. The effect of permeability enhancer on the permeability of drug from cellulose acetate and ethyl cellulose patches was studies. The polymeric combinations showed good film forming properties and the method of casting on mercury substrate was found to give good films. Patel et al., (2009) have studied transdermal patches containing glibenclamide (1.06 % w/v, i.e. 13.5 mg/cm2) were prepared by solvent casting technique employing mercury as substrate to formulate transdermal patches using Eudragit RL 100, Eudragit RS 100, Polyvinyl pyrollidone (PVP) as polymers, glycerol and propylene glycol as a plasticizers and Span 80 as a permeation enhancer by solvent casting method. The formulation containing Eudragit RL 100 with propylene glycol as plasticizer showed complete and prolonged release with 98.02% at the end of 24 h.

4.4 "IPM membranes" method

The drug is dispersed in a mixture of water and propylene glycol containing carbomer-940 polymers and stirred for 12 h in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of tri-ethanolamine. Buffer (pH 7.4) can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will incorporated in the IPM (isopropyl myristate) membrane (Tang et al., 2010). Xi et al., (2010) have studied the drug-in-adhesive transdermal patch and evaluated for the site-specific delivery of anastrozole. Different adhesive matrixes, permeation enhancers and amounts of anastrozole were investigated for promoting the passage of anastrozole through the skin of rat in-vitro. The best skin permeation profile (in-vitro) was obtained with the formulation containing DURO-TAK® 87-4098 (pressure sensitive adhesive), IPM 8% and anastrozole 8%. For local tissue disposition studies, the anastrozole patch was applied to mouse abdominal skin, and blood, skin, and muscle samples were taken at different times after removing the

residual adhesive from the skin. High accumulation of the drug in the skin and muscle tissue beneath the patch application site was observed in mice and compared with that after oral administration. These findings showed that anastrozole transdermal patches were an appropriate delivery system for application to the breast tumour region for site-specific drug delivery to obtain a high local drug concentration.

5-WHY TDDS for hypertension

Developing controlled drug delivery has become increases the importance in the pharmaceutical industry. Today about ¾th % (75%) of drug are taken orally but it are not found be as effective as desired. To improve such character transdermal drug delivery system was emerged as Novel drug delivery system. Transdermal drug delivery represents one of the most rapidly advancing areas of novel drug delivery because it overcomes the difficulties of oral antihypertensive drugs.

TDDS have many advantage over conventional antihypertensive drug delivery such as noninvasive, ease of use, withdrawn (increases side effect), avoid first pass metabolism, best patient compliance, no need of hospitalizations, avoid gastric irritation, reducing dosing frequency of drug. Hence TDDS was selected for the treatment of hypertension.

Hypertensive is a disease characterized by persistently high blood pressure. Hypertension is one of the largest deaths causing disease for the human being. Since it is a chronic disease so it necessitates long term treatment. Hypertensive a cardiovascular disease account for a large proportional of all death and disability worldwide. Hypertensive is directly responsible for 57% of all strokes death and 24% of coronary heart disease in India. Transdermal system is ideally suited for disease that demand chronic treatment. In this project TDDS are mainly used for the delivery of antihypertensive drug from transdermal patches.[21]

Telmisartan is a angiotensin II receptor antagonist, Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT1 receptor by binding reversibly and selectively to the receptor in vascular smooth muscle and adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis of and release of aldosterone, blockage of its result in decrease vascular resistance hence B.P falls.[22]

5.1-Some antihypertensive drugs in form of TDDS are

5.1.1 Carveliolol-It is a B1+B2+alpha1 adreno receptor blocker having oral bioavailability 30% while transdermal patch bioavaibility of 75%.

5.1.2 Metoprolol-It is a prototype of cardioselective B1-blocker and is incompletely absorbed with oral bioavailability 35% while it shows higher percentage of drug release in case of transdermal patch.

6-CONCLUSION

TDDS are topically administrated medicament which release the drug into the systemic circulation through the skin for systemic effects at a predetermined rate and controlled rate .In case of hypertension ,transdermal patches helps in providing optimum amount of drug to control the condition by reducing the dosing frequency This review shows that antihypertensive drug by this route improves bioavailability as well as patient compliance and also lead to cost effectiveness of health care.

7-ACKNOWLEDGEMENT

The authors express gratitude to GRD(PG)IMT and Director of pharmacy Dr.N.G.Raghavendra Rao and Prof. Yogita Tyagi for their kind support in providing all facilities related to this manuscript.

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